Neuropsychiatric Symptoms as Predictors of Falls in Long-Term Care Residents With Cognitive Impairment

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Abstract

*Objectives***:** Falls and neuropsychiatric symptoms (NPS) are common among long-term care residents with cognitive impairment. Despite the high prevalence of both falls and NPS, little is known about their association. The aim of our study was to explore how NPS, particularly the severity of NPS and specific NPS subgroups, are associated with falls and how psychotropics modify this association.

*Design***:** Longitudinal cohort study.

Setting and Participants: 532 long-term care residents aged 65 years or over in Helsinki, Finland.

Methods: NPS were measured with Neuropsychiatric Inventory (NPI) at baseline. Participants were grouped into three groups: no significant NPS (NPI points 0-3), low NPS burden (NPI 4-12) and high NPS burden (NPI>12). The number of falls, injuries, fractures, and hospitalizations were collected from medical records over 12 months following baseline assessment.

Results: Altogether 606 falls occurred during the follow-up year. The falls led to 121 injuries, 42 hospitalizations, and 20 fractures. Falls and injuries increased significantly with NPS burden ($p<0.001$): 330 falls in the high NPS group (n=184), 188 falls in the low NPS group (n=181) and 88 falls in the no significant NPS group (n=167). The risk of falling showed a curvilinear association with NPI total score. Of NPS subgroups, psychosis and hyperactivity were associated with a higher incidence rate ratio of falls, whereas apathy had a protective association even after adjustment for age, sex and mobility. Affective symptoms were not associated with falls. Psychotropics did not modify the association between NPS burden and falls.

*Conclusions and Implications***:** The results of this study show that NPS, especially NPS severity, may predict falls and fall-related negative consequences. Severity of NPS should be taken into account when assessing fall risk in long-term care residents with cognitive impairment.

Keywords: falls– neuropsychiatric symptoms – cognitive impairment – Neuropsychiatric Inventory – long-term care

Introduction

Falls and fall-related negative consequences among long-term care residents with cognitive impairment are common.[1-4] An estimated 37-65% of older people with cognitive impairment or dementia fall annually.[5-6] The risk factors for falls are multiple and seem to vary between community- and institution-dwelling older adults with cognitive impairment.[3, 6-7] Impaired mobility, use of psychotropic drugs, anxiety, depression and orthostatic hypotension have been shown to increase fall risk.[4, 7-12]

Neuropsychiatric symptoms (NPS), also called behavioral and psychological symptoms of dementia (BPSD), are known to be highly common in cognitive impairment, especially in long-term care settings. The prevalence of NPS in long-term care has been estimated to be as high as 82-92%.[13-14] NPS include such symptoms as agitation, apathy, anxiety, aberrant motor behavior, delusions, dysphoria, disinhibition, euphoria, hallucinations, and irritability.[15] Cluster analyses have identified four NPS subgroups: hyperactivity, psychosis, affective symptoms, and apathy.[16]

Despite the high prevalence of both NPS and falls among older adults with cognitive impairment in long-term care, little is known about the association between NPS and falls. A few studies have suggested NPS to be an independent risk factor for falls.[17-22] However, it is not known whether severity of NPS has an impact on fall rate. Thus, the aim of our study was to explore how NPS, and more specifically the severity of NPS, are associated with falls and their consequences. Another aim was to determine how specific NPS subgroups impact the incidence of falls.

Methods

Study participants

Participants were recruited to this longitudinal cohort study from institutional settings in Helsinki in 2017. From a random sample from 18 nursing homes, 544 volunteer residents were recruited to this study. Participants' baseline assessment occurred between February 2018 and August 2018. All

participants who completed the Neuropsychiatric Inventory (NPI) at baseline (n=532) were included in the study. The participants were followed for 12 months or until death.

Measures

Study nurses were trained to perform the assessments. One of the researchers (HMR) participated in and supported the nurses in the baseline assessments and data collection. Data on demographic factors such as age, sex, and diagnoses, were collected from medical records. The study nurses calculated the Charlson Comorbidity Index[23] to assess each resident's burden of comorbidity and the Barthel Index[24] for functional evaluation. Mobility was assessed by the 15D questionnaire[25] item on mobility and categorized into one of the following: 1) "able to walk without help outdoors or indoors", 2) "able to walk indoors only with help from others", or 3) "completely bed-ridden and unable to move about." Mini Mental State Examination (MMSE)[26] and Clinical Dementia Rating (CDR)[27] were performed to assess the severity of cognitive impairment. Presence of vision and hearing deficits were assessed by 15D questionnaire[25] items on vision and hearing. Vision was categorized into either 1) "able to read papers and/or TV text with or without glasses" or 2) "not able to read papers or TV text either with glasses or without. Hearing was categorized into either 1) "able to hear speech with or without a hearing aid with normal or louder than normal voice or 2) "able to hear even loud voices poorly or deaf".

Data on medication use were retrieved from medical records on the assessment day. All medications were classified using the Anatomical Therapeutic Chemical (ATC) classification system.[28] Psychotropic medications included antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), and hypnotics and sedatives (N05C). The use of Alzheimer medication (N06D) included cholinesterase inhibitors (N06DA) and/or memantine (N06DX01). Only regularly used medications were considered. Medication use was considered regular if there was a documented regular sequence of administration.

To evaluate NPS, study nurses interviewed care staff from the long-term care units using the NPI.[29] The NPI was chosen instead of NPI-NH, because the nursing home version has not been translated to Finnish language. The content of the questions of the NPI and NPI-NH are identical. NPI includes 10 different NPS (agitation, apathy, anxiety, aberrant motor behavior, delusions, dysphoria, disinhibition, euphoria, hallucinations, irritability). For each symptom, the severity is multiplied by the frequency, and the sum score provides the total NPI score (range 0 to 120). Subgroups of "Psychosis" (delusion, hallucinations), "Hyperactivity" (agitation, euphoria, disinhibition, irritability, aberrant motor behavior), "Affective symptoms" (depression, anxiety), and "Apathy" (apathy) were calculated separately, as earlier described[16]. We grouped the residents according to the total score on NPI into three groups: no significant NPS (NPI 0-3), low NPS burden (NPI 4-12), and high NPS burden (NPI >12). According to previous studies, a score >3 is taken to indicate the presence of clinically relevant symptoms.[29] The cut-off point of 12 was chosen as it was the median. In previous studies a total NPI score greater than 11 points arising from at least three domains has been considered to indicate marked neuropsychiatric symptoms.[30] After baseline assessment, data regarding falls (number of falls, injuries, fractures, and hospitalizations) were collected from medical records during the 12-month-follow-up. Mortality was retrieved from central records.

Statistics

Data are presented as means with standard deviation (SD) or as counts with percentages. The statistical significance for the unadjusted hypothesis of linearity across categories (tertiles) of NPI total score and characteristics of study participants was evaluated using the Cochran-Armitage test for trend, analysis of variance (ANOVA), and logistic (ordinal) models with an appropriate contrast. A bootstrap method was used when the theoretical distribution of the test statistics was unknown or in case of violation of assumptions (e.g. non-normality). We used the Kaplan-Meier method to

construct estimated mortality. Cox proportional Hazard Model was used to estimate age, sex and mobility adjusted risk (HR) for mortality between the groups. The number and incidence rate of falls were calculated assuming a Poisson distribution. Adjusted incidence rate and incidence rate ratio (IRR) were calculated using a Poisson regression model that included sex, age and mobility as covariates. Multivariate Poisson regression models with forward stepwise was used to investigate factors related to incidence of falls. Variables significant at the $P<0.10$ level in unadjusted analyses were included into the model. Multivariate Poisson regression was tested using goodness of fit of the model, and the assumption of overdispersion in the Poisson model was tested using the Lagrange multiplier test. A possible non-linear relationship between all falls and the NPI total score was assessed by using a 3-knot-restricted cubic (placed according to Harrell's recommended percentiles) spline Poisson regression model. The normality of variables was evaluated graphically and using the Shapiro–Wilk W test. Stata 16.0 (StataCorp LP, College Station, TX, USA) was used for the analysis.

Statement of ethics

The study protocol was approved by the Ethics Committee [redacted] Written informed consent was obtained from each participant and in case of significant cognitive decline (CDR 2 or 3) from their closest proxy.

Results

The three NPI groups were similar in baseline demographic characteristics such as age, sex and Charlson Comorbidity Index (Table 1). Residents' mean age was 85 years, 80% were women and the mean number of comorbidities according to the Charlson Comorbidity Index was 2.1. Significant differences between the groups were detected in functional capacity according to the

Barthel Index and in mobility. The residents with the highest NPS burden were the most mobile and had better functioning than residents with no significant NPS (p<0.001). Two of three residents suffered from severe cognitive impairment (CDR 3) and the mean MMSE was low, 6.8. No significant differences existed between groups in severity of cognitive impairment according to MMSE (p=0.89) or CDR rating (p=0.35).

The NPI groups differed significantly in psychotropic medication use (p<0.001). Mean number of psychotropic medications in the high NPS burden group was 2.3, compared with 1.8 in the group with no significant NPS. The proportion of residents taking any psychotropic medication was very high, 87%. Residents with high NPS burden were also administered more often Alzheimer's medication (p=0.041) and had a higher number of total medications 8.8, compared with 7.9 in the group with no significant NPS (p=0.031). The most common NPS subgroup was hyperactivity in all NPI groups.

Mortality and incidence of falls according to NPI total score during follow-up

Total follow-up time was 446.8 person-years, with the mean time being 0.84 (range 0.01 – 1.00) years per person. During the one-year follow-up the mortality was 28.7% in the group with no significant NPS, 33.2% in the low NPS burden group, and 33.7% in the high NPS burden group (p=0.56). When the NPI 0-3 group was used as reference age, sex and mobility adjusted HR for mortality in NPI 4-12 group was 1.08 (95% CI 0.73 – 1.60) and in NPI >12 group 1.19 (95% CI 0.80 – 1.79).

Altogether 606 falls occurred during the follow-up: 330 in the high NPS burden group, 188 in the low NPS burden group and 88 in the no NPS group (Table 2). Of 532 residents, one-third fell at least once (94 residents). Severity of NPS measured by NPI total score had a curvilinear association with the incidence rate of falls per person years (Figure 1). Using the no significant NPS group as a reference, the low NPS burden group had an IRR per SD for falls of 1.64 (95% CI 1.27 – 2.12,

adjusted for age, sex and mobility), whereas in the high NPS burden group the IRR per SD was 2.43 (95% Cl 1.91 – 3.08, adjusted for age, sex and mobility) (p for linearity < 0.001).

The associations between NPS subgroups and the IRRs of falls and fall-related negative consequences are presented in Figure 2. Psychosis and Hyperactivity subgroups were associated with a higher IRR of falls and injuries, whereas Apathy showed a protective association against falls but not injuries. Affective symptoms did not predict falls nor injuries. Psychosis, Hyperactivity and Affective symptom subgroups were associated with a higher IRR of hospitalizations, whereas Apathy was not. None of the subgroups predicted fractures (Figure 2).

Falls and fall-related negative consequences during the 12-month follow-up

Of 606 falls, 121 led to injuries, 42 to injuries needing hospitalization, and 20 to fractures. Falls and injuries increased significantly with NPS burden (p<0.001). Residents with a higher NPI total score were also more often hospitalized for their falls than residents with no significant NPS or with a low NPS burden (p=0.002). The number of fractures increased in the higher NPI groups but it did not reach statistical significance (p=0.16) (Table 2).

In a multivariate poisson regression analysis a higher NPI level ("NPI 4-12" IRR 1.72, 95% Cl 1.33 to 2.23; "NPI >12" IRR 2.58, 95% Cl 2.03 to 3.29) and male gender (IRR 1.80, 95% Cl 1.51 to 2.16) were associated with a higher incidence of falls. Worse mobility ("able to walk only with help" IRR 0.57, 95% Cl 0.47 to 0.69; "bed-ridden" IRR 0.10, 95% Cl 0.07 to 0.15), age (IRR 0.98, 95% Cl 0.97 to 0.99) and the use of psychotropic medication (IRR 0.88, 95% Cl 0.83 to 0.94) were associated with a lower incidence of falls. Alzheimer's medication (IRR 1.12, 95% CI 0.94 to 1.33) and hearing decifits (IRR 0.76, 95% CI 0.45 to 1.26) were not associated with incidence of falls (Table 3).

Finally, we stratified the residents according to their psychotropic use to see how psychotropics modified the association between NPS severity and incidence rate of falls. NPI level was associated with incidence rate of falls per person-years ($p<0.001$ for NPI level), whereas psychotropic drug use did not have a significant association ($p=0.94$ for psychotropic), and no interaction existed ($p=0.57$ for interaction) (Figure 3).

Discussion

NPI total score of long-term care residents with cognitive impairment showed a curvilinear association with the incidence rate of falls, indicating that severity of NPS is associated with risk of falls. Even after adjustments, IRR per SD in the high NPS burden group was nearly 2.5-fold that in the no significant NPS group. Psychotropic drug use did not modify this association. Another important finding was that, of all the NPS subgroups, specifically Psychosis and Hyperactivity had the highest association with fall rate, while Apathy seemed to have a protective association.

The results of this study are in line with the few previous reports examining the association between NPS and falls.[17-22] According to our study, the fall risk related to NPS seems to particularly arise from hyperactivity and psychotic symptoms. A population-based study from Sweden in 2005 also found that having hyperactive symptoms was one of the factors most strongly associated with falls.[1] The results from earlier studies regarding wandering are contradictory. A systematic review from 2013 found wandering to be protective against falls[3], whereas more recent studies have suggested that wandering increases the risk for falls.[22, 31] In our study, affective symptoms and apathy were not associated with an increased fall risk. This could be due to less day-time activity offering less opportunities for falling.

The findings from previous studies indicate that both NPS and falls increase with the severity of cognitive impairment.[32-35] In our study, there was no difference in the severity of cognitive impairment between the three NPI groups measured by MMSE or CDR. This could be due to the

222 characteristics of our study population, with cognitive impairment being severe in all three groups.
223 The NPI group with no significant NPS had the largest proportion of bed-ridden residents. An
224 interesting finding was that the residents with the highest NPS burden at baseline also had the best
225 mobility and the highest number of falls. This seems logical as these residents are physically more
226 active during the day, thus having more opportunities to fall. This is in line with earlier research on
227 fall risk in long-term care.[20] However, even after adjustment for mobility, the severity of NPS
228 remained significantly associated with higher incidence of falls, indicating that NPS burden is an
229 independent predictor for falls.

230 The use of psychotropic medication in our study population was very high in all groups. However,
231 there were significant differences in the number of psychotropics used in each NPS group. The
232 group with highest NPS burden also had the highest number of psychotropics (2.3), compared with
233 the groups with low NPS burden (2.1) and no significant NPS (1.8). Several earlier studies suggest
234 that psychotropic medication use increases the risk of falls.[36-38] To gain more insight into this
235 relationship, we looked at the differences in fall rates among residents with and without
236 psychotropic drug use. In our study, only NPI level was associated with incidence rate of falls,
237 psychotropic drug use was not. There was no interaction indicating that psychotropic drug use did
238 not modify this relationship. Our study suggests that in this special long-term population with
239 severe cognitive impairment, the NPS burden is more important in determining falls than
240 psychotropic drug use.

241 In our study one-third of all falls during the one-year follow-up led to fall related negative
242 consequences (20% to injuries, 7% to hospitalizations, 3% to fractures). This result is consistent
243 with previous studies that have found that most falls do not result in injury. [4, 8, 20] Even though all
244 falls do not lead to injury, every fall is significant as a previous fall is an important risk factor for
245 another fall.[39]

Our study has some limitations that should be considered when interpreting the results. First, we did not ask about the use of physical restraints. It is well known that, despite clear evidence for a lack of effectiveness and safety, physical restraints are frequently used in nursing homes and their use is associated with falls.[40-41] Another limitation is that only regularly used psychotropic medication was considered in our study. Psychotropics administered "pro re nata" may have had a different impact on falls and their consequences. Finally, as a longitudinal follow-up study of a special cohort, we cannot rule out unknown confounders having an effect on falls. Additionally we do not have data on past fall history.

Our study has several strengths. The study sample is large and representative of older long-term care residents with cognitive impairment. We used many well-validated assessment instruments, and data were collected by trained study nurses resulting in high data validity. Another important strength is that, to our knowledge, no other study has previously examined the impact of severity of NPS on fall rate, nor has the association between NPS subgroups and fall rate or the interaction of severity of NPS and psychotropics with falls been investigated.

Conclusions and Implications

Most falls are not the result of a single cause, but occur due to an interaction of several risk factors. Thus, a multifactorial approach to fall prevention is recommended. The findings of this study indicate that evaluation of NPS, and especially severity of NPS, and NPS subgroups should be part of the comprehensive assessment when aiming to prevent falls in long-term care residents with cognitive impairment.

The authors declare that they have no conflicts of interest relevant to this report.

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Table 1. Characteristics of residents grouped by severity of neuropsychiatric symptoms according to Neuropsychiatric Inventory (NPI) total score

Table 2. Falls and fall-related negative consequences during the 12-month follow-up

Table 3. Multivariate poisson regression analysis for incidence of falls.

Figure 1. Incidence of falls per person-years (pyrs) according to Neuropsychiatric Inventory (NPI) total score. Adjusted for age, sex and mobility.

Figure 2. Association between neuropsychiatric symptoms subgroups and incidence rate ratio (IRR) of falls and fall related negative consequences per 1-SD. Adjusted for age, sex, and mobility.

Figure 3. Incidence rate of falls during the 12-month follow-up per person-years (pyrs) among residents with and without psychotropic medication according to Neuropsychiatric Inventory (NPI) level.